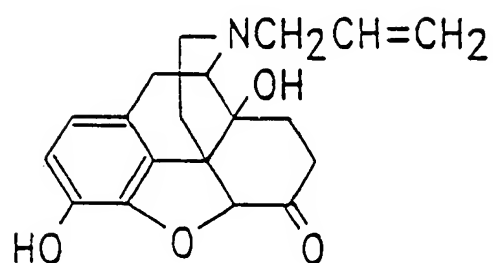
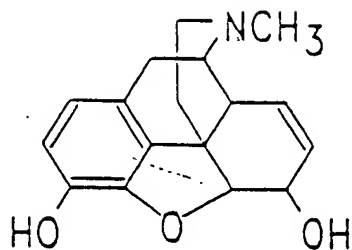
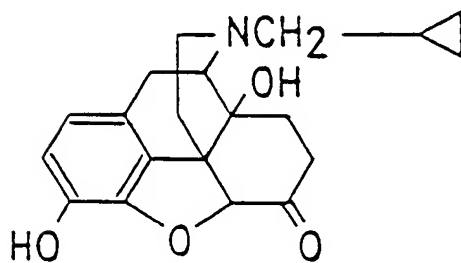


APPROVED	O.G. FIG. —
BY	CLASS SUBCLASS
DRAFTSMAN	514 285

Morphine



Naloxone



Naltrexone (R=O)
Nalmefene (R=CH₂).

FIG. 1

10037791.010302

APPROVED	O.G. FIG. —
BY	CLASS
DRAFTSMAN	SUBCLASS
	574 285

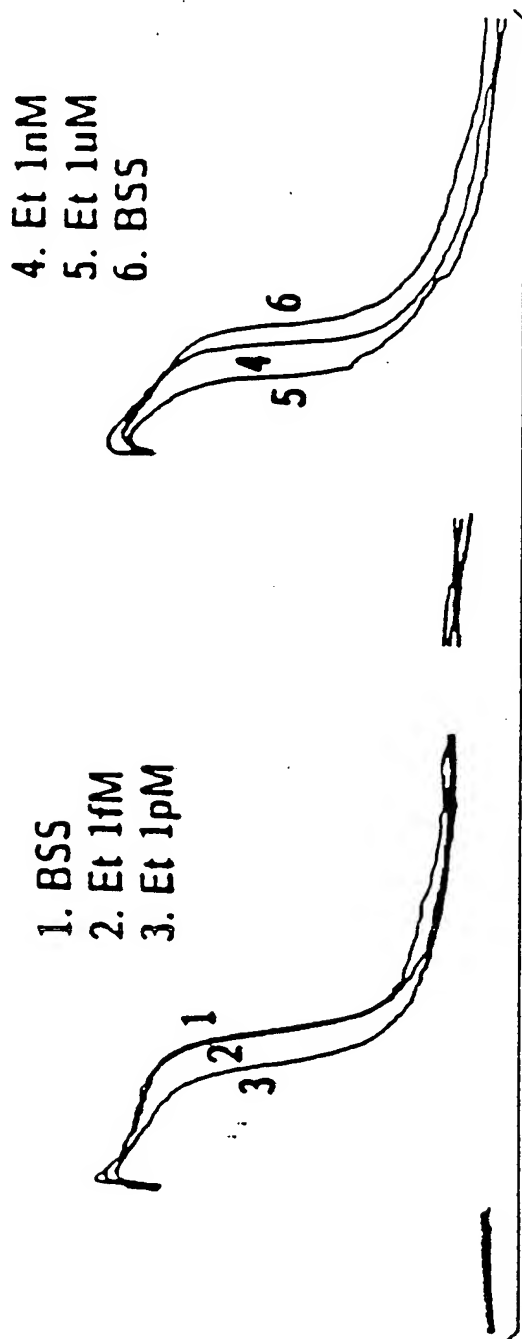


FIG. 2A

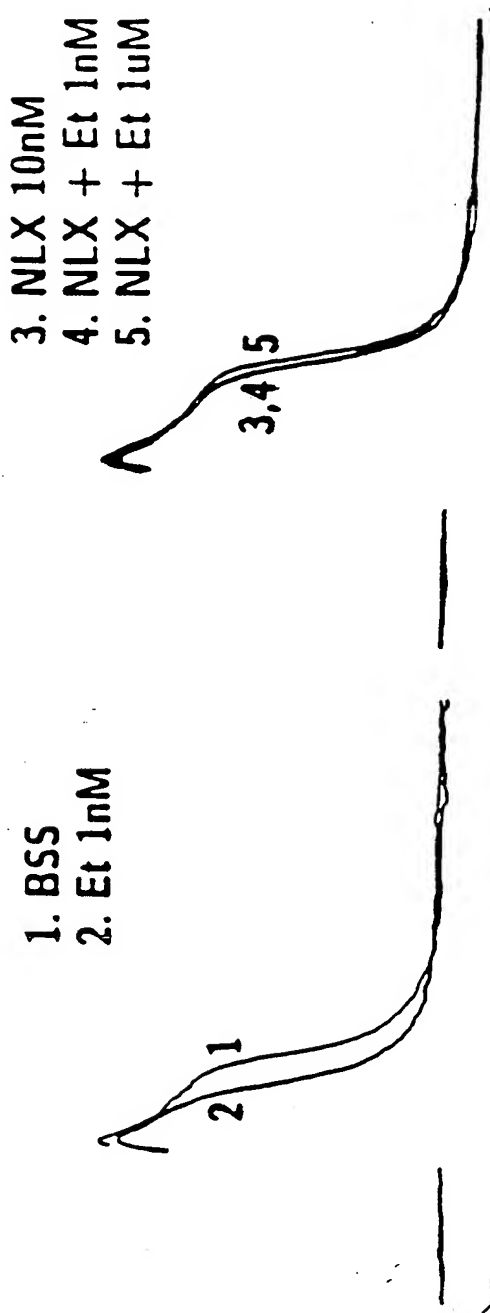


FIG. 2B

20EOT10" T644E00T

APPROVED	O.G. FIG.	
BY	CLASS	SUBCLASS
DRAFTSMAN	514	285

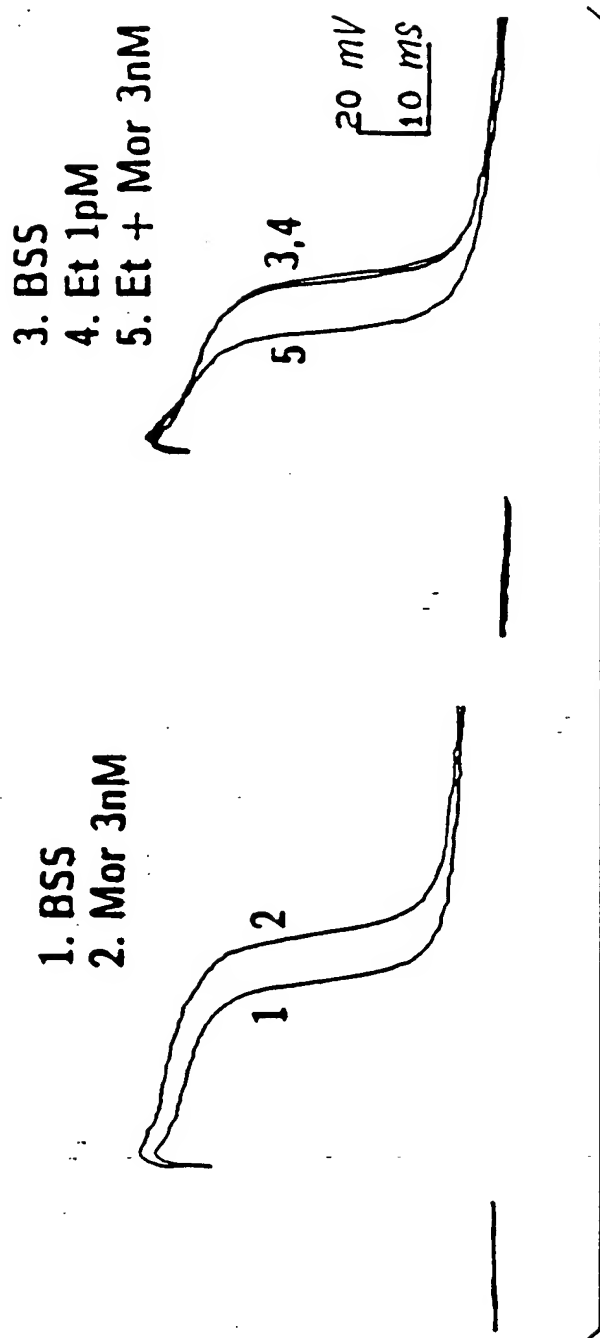


FIG. 2C

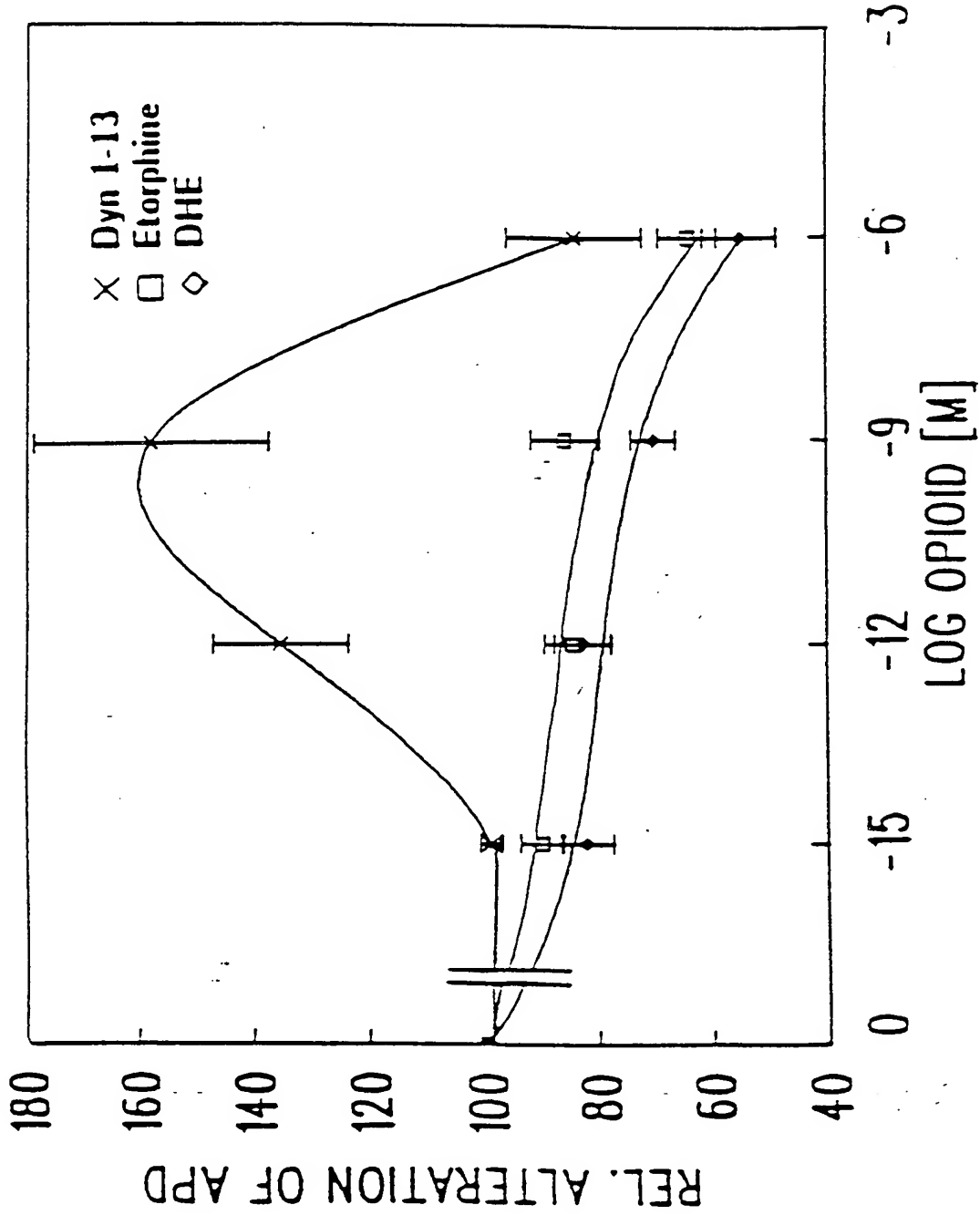
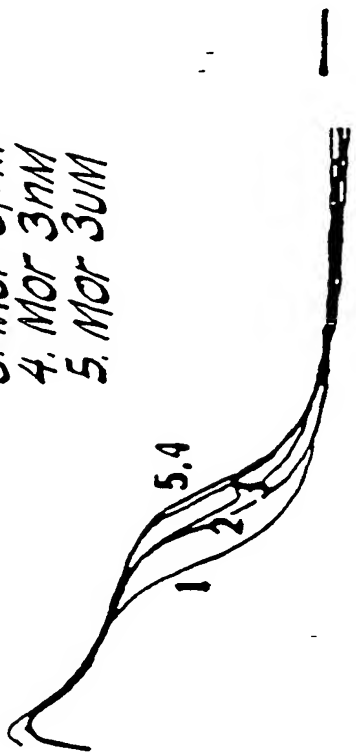


FIG. 3

20EOTD" T642EOTF

APPROVED	O.G. FIG. —
BY	CLASS SUBCLASS
DRAFTSMAN	514 285

1. BSS
2. MOR 3fM
3. MOR 3pM
4. MOR 3nM
5. MOR 3uM



6. BSS
7. DPN 1pM
8. DPN + MOR 3fM
9. DPN + MOR 3pM
10. DPN + MOR 3nM
11. DPN + MOR 3uM

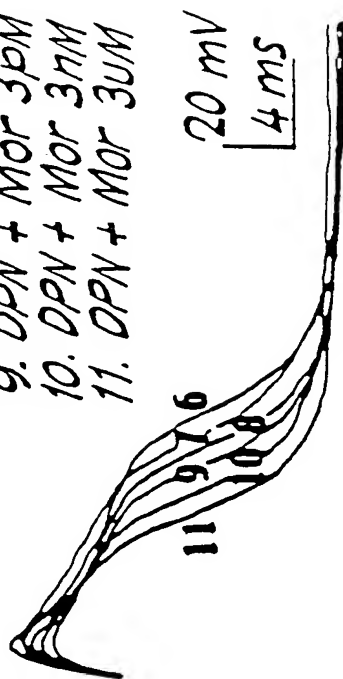


FIG. 4A

202070" T644E00T

APPROVED	OG. FIG. —	
BY	CLASS	SUBCLASS
DRAFTSMAN	T14	285

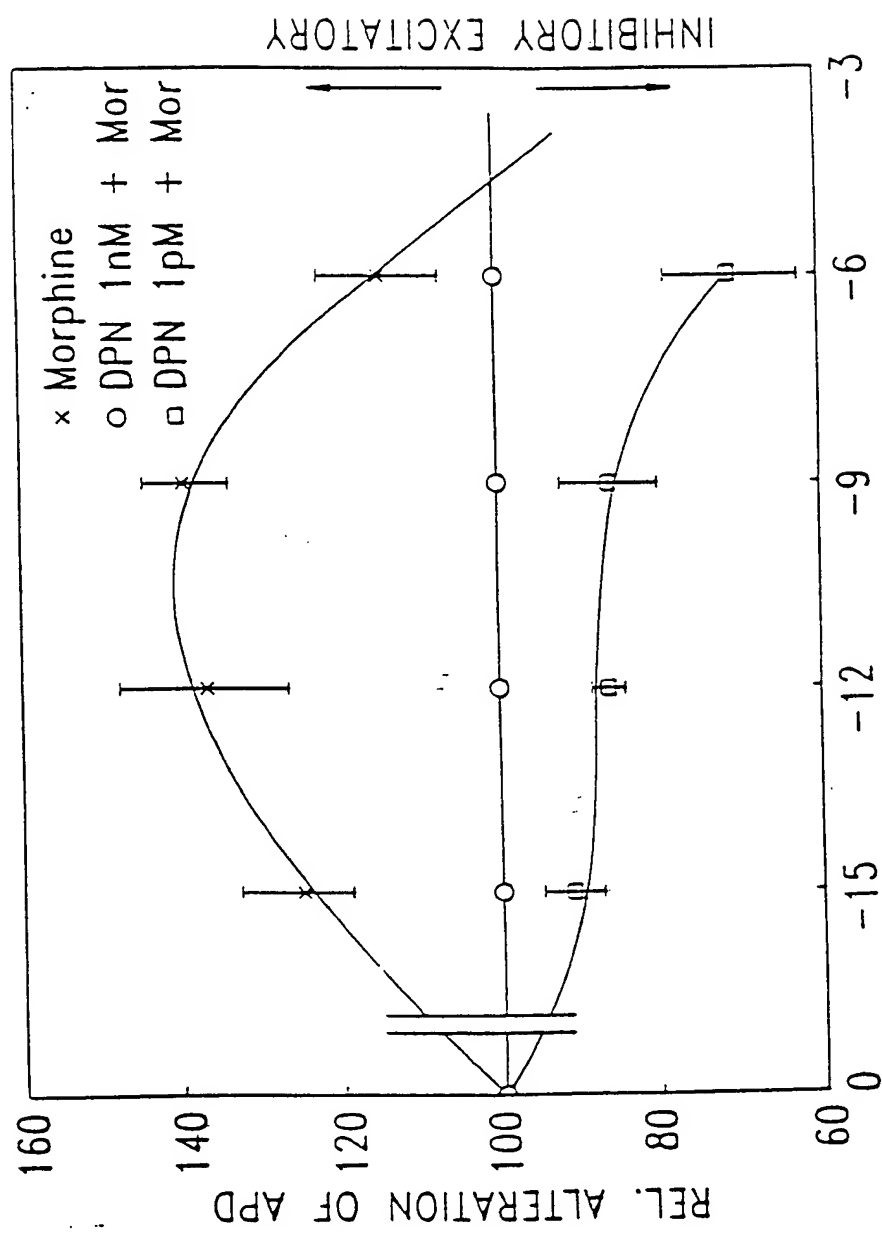


FIG. 4B.

20E0TD" T644E0DT

APPROVED	O.G. FIG. —	
BY	CLASS	SUBCLASS
DRAFTSMAN	716	285

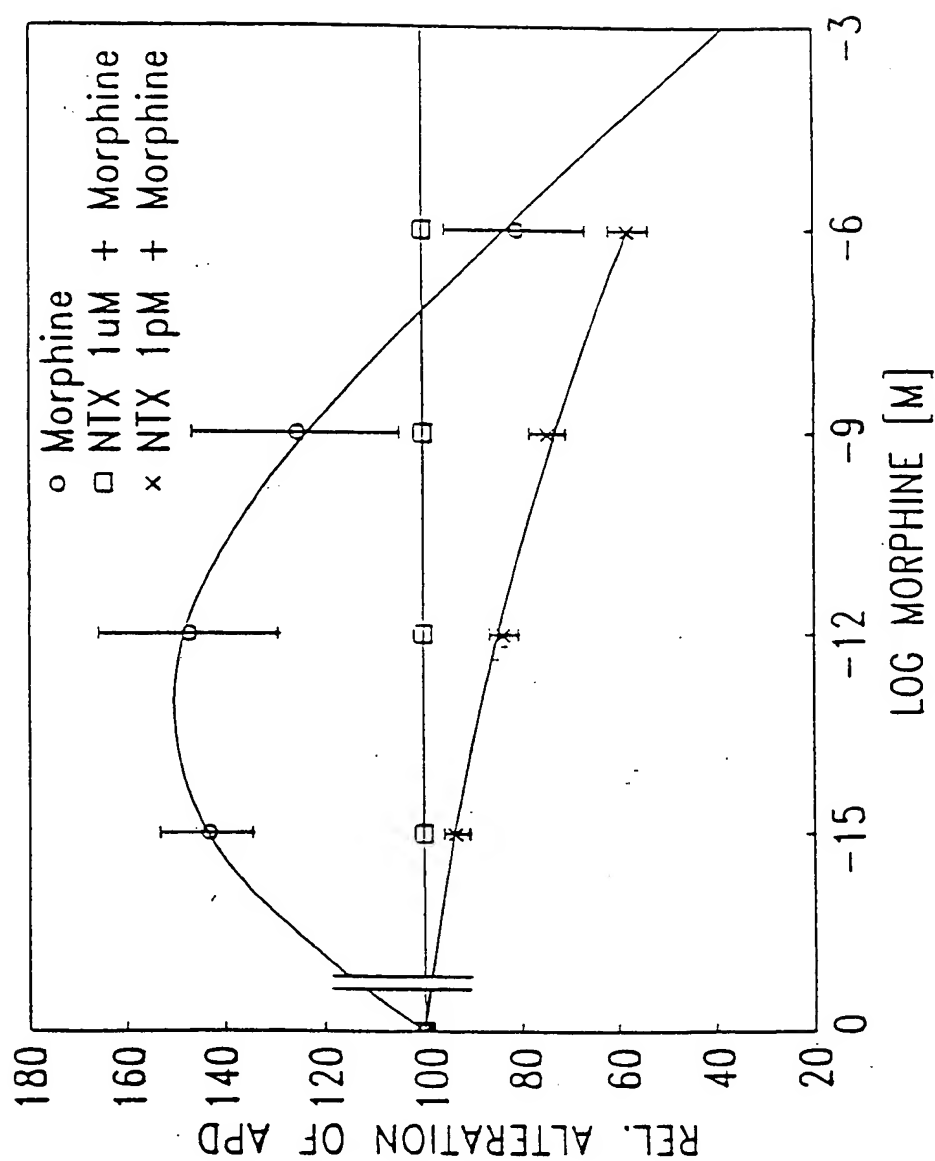


FIG. 5

20200707 164400

Alteration of Action Potential Duration (APD)				
(APD shortening: ↓ ;APD prolongation: ↑ ;No APD change: 0)				
Acute Test	Naive DRG Neurons		Chronic Morphine-Treated Neurons (1uM; >1wk)	Chronic Co-treatment with Mor + Antag. at Excit. Op. Rec. (pM)
	Control BSS	BSS + Antag. at Excit.Op.Rec. (pM)		After Washout with BSS
1 - 10 uM morphine	↓ (inhibitory) ("analgesia")	↑↑	↑ ("tolerance")	↑
pM - nM morphine	↓ ("excitatory antianalgesia")	↓ (unmasking of inhibitory effects)	↑	↑
~ fM morphine or dyn A-(1-13)	0	0	↓ (excitatory supersensitivity)	0
nM naloxone	0	0	↓ ("dependence") ("withdrawal effect")	0

FIG. 6

APPROVED	O.G. FIG. —
BY	CLASS
DRAFTSMAN	SUBCLASS
714	285

Co-Treatment with Low-dose Naltrexone Enhances
Morphine's Antinociceptive Potency

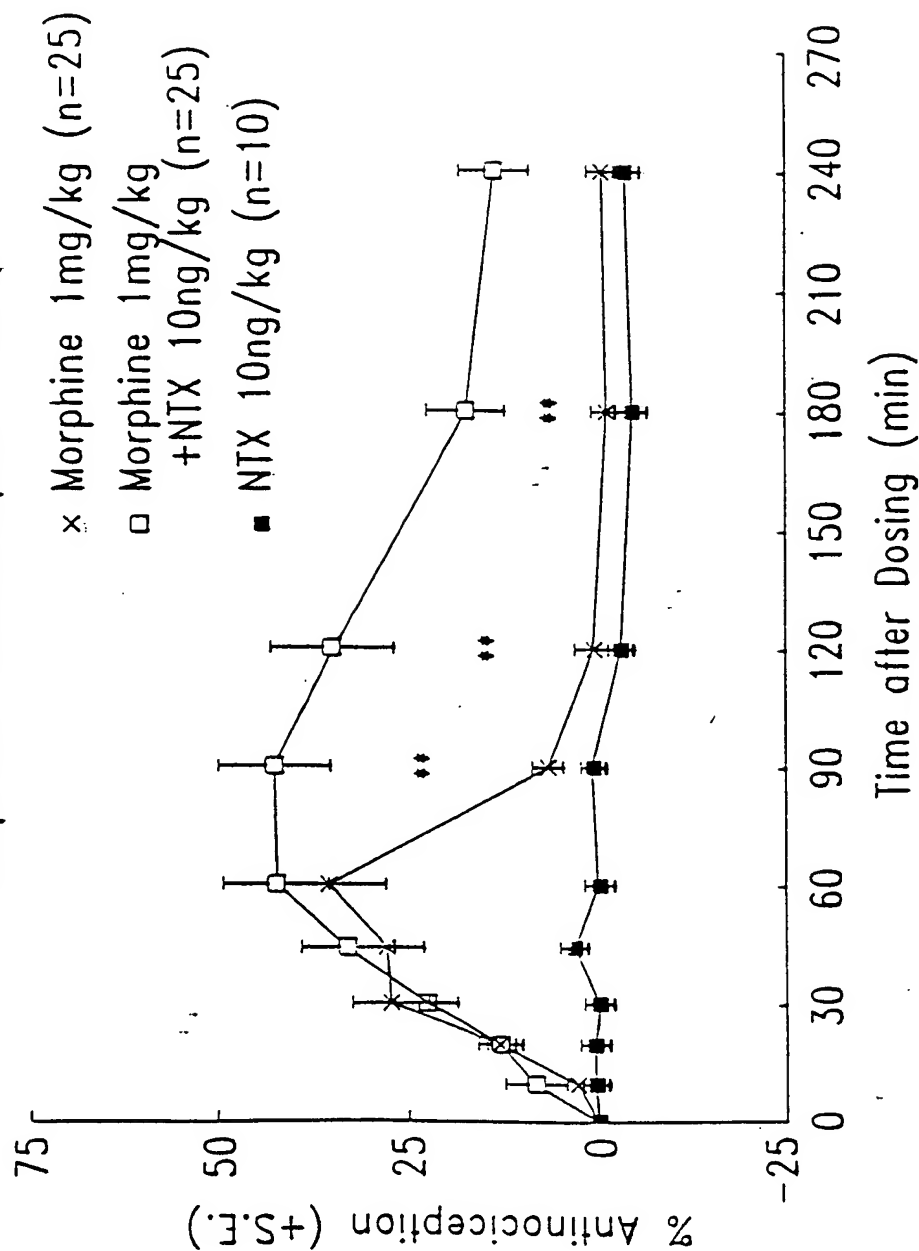


FIG. 7

206070" T644E001

Co-Treatment with Low-Dose Naltrexone Attenuates Acute and Chronic Morphine Dependence

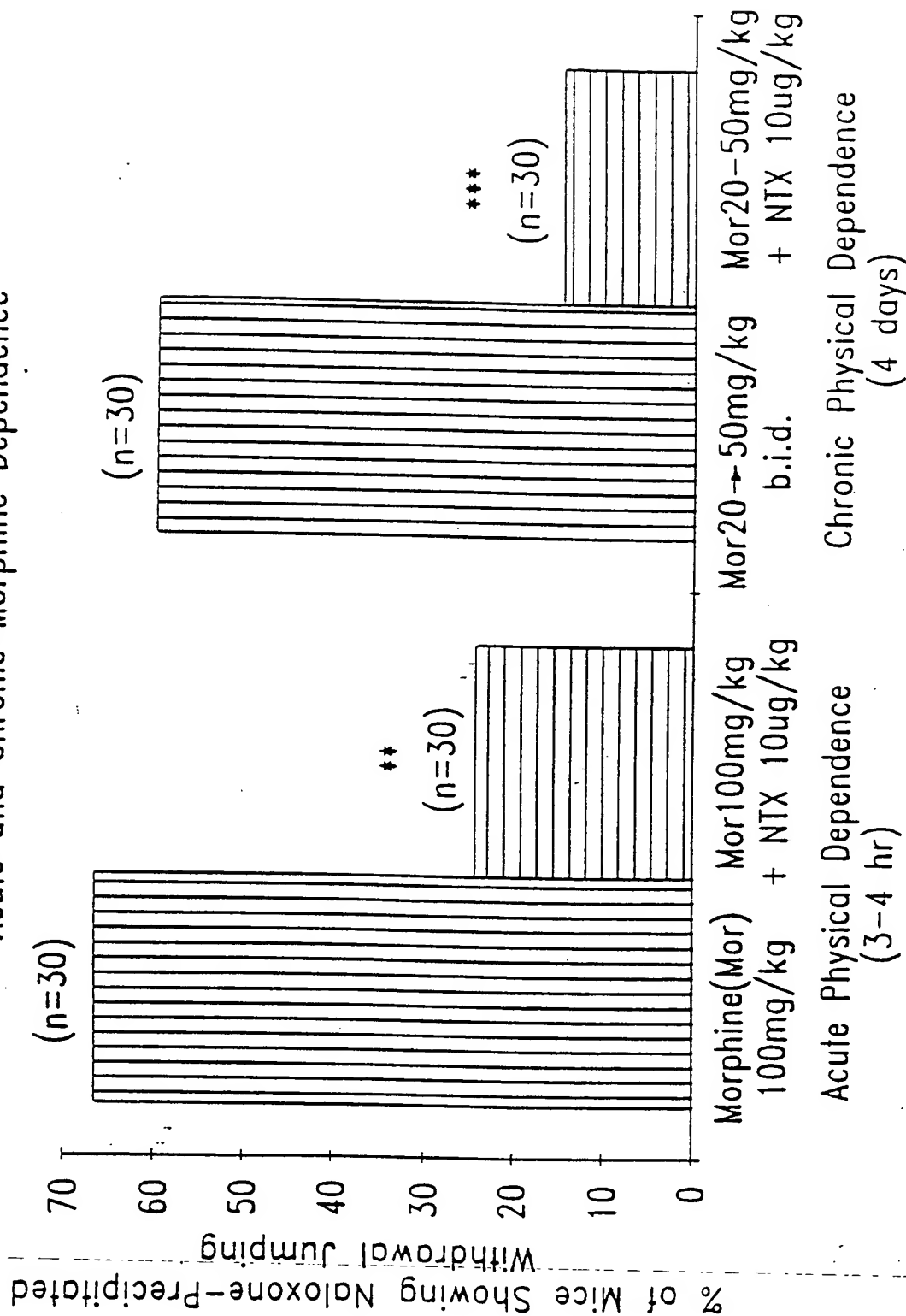


FIG. 8

APPROVED	O.G. FIG. —	
BY	CLASS	SUBCLASS
DRAFTSMAN	574	28.5

Co-Treatment with Ultra-Low Dose Nalmefene Enhances Morphine Antinociceptive Potency

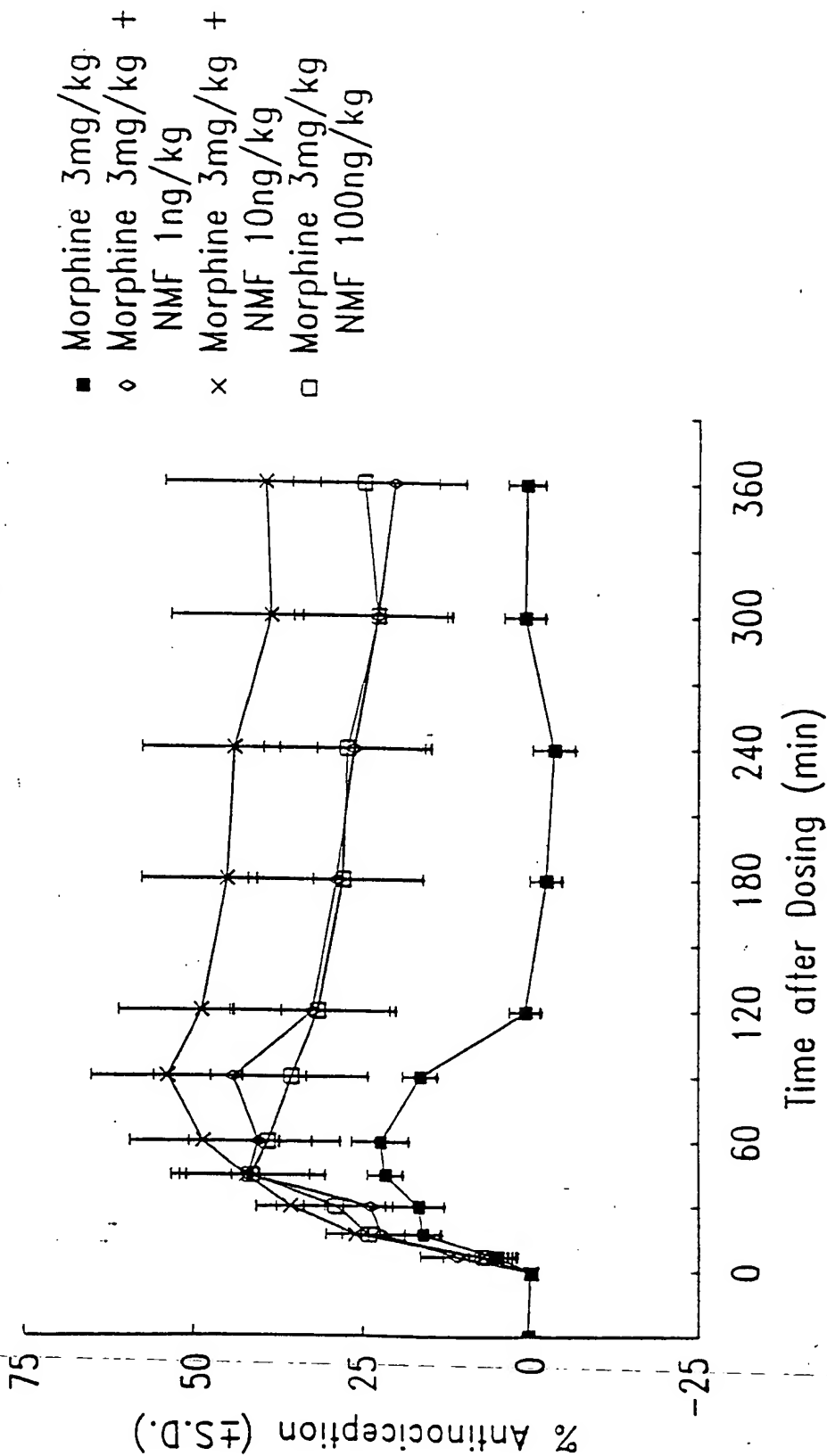


FIG. 9

20E0T0" T644E00T

APPROVED	O.G. FIG.	—
BY	CLASS	SUBCLASS
DRAFTSMAN	514	285

Co-Treatment with Low-Dose Naltrexone or Nalmefene
Attenuates Acute Morphine Dependence

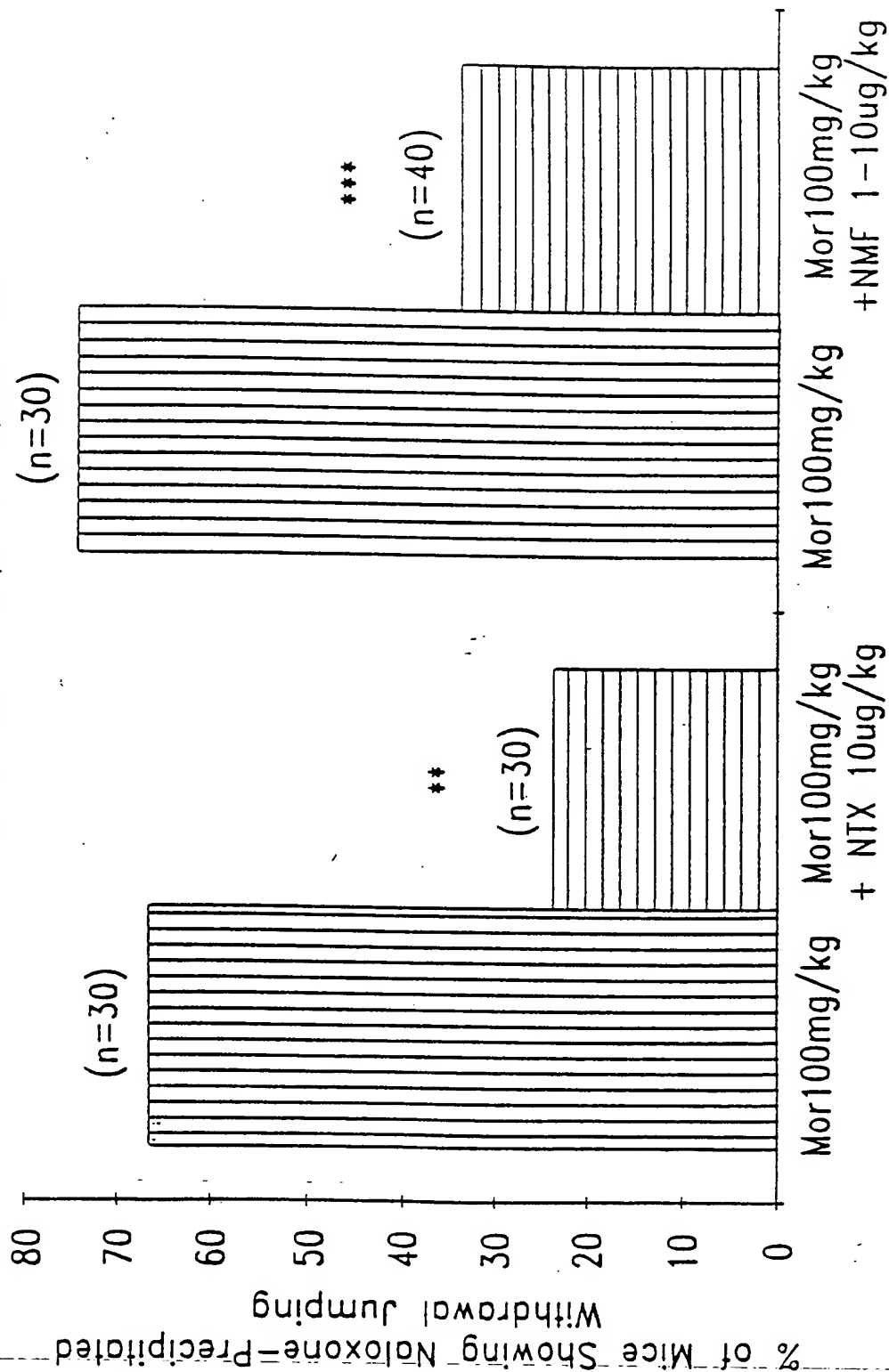


FIG. 10